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Referral for lung transplantation: experience of a Birmingham Adult Cystic Fibrosis Centre between 1987 and 1994

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Abstract

***Background* – Whilst much is known of the outcome of lung transplantation for patients with cystic fibrosis, less is known about those patients who are either not referred for transplantation or who die before a donor is available. The referral practice and outcome of all the cystic fibrosis patients in one clinic was documented, whether or not they were assessed for lung transplantation. The results give a perspective on the impact of the current transplantation programmes on the adult cystic fibrosis population as a whole.**

***Methods* – A retrospective study was made of patient deaths and referrals for lung transplantation between 1987 and 1994 from the Adult Cystic Fibrosis Clinic at Birmingham Heartlands Hospital.**

***Results* – The Birmingham Heartlands Adult Cystic Fibrosis Clinic has managed 192 patients since its beginning and currently cares for 141 patients. Since 1987 there have been 16 deaths in patients with cystic fibrosis who were considered unsuitable for lung transplantation. Of 49 patients referred for lung transplantation, 47 were accepted on to a provisional or active waiting list. The mean (SE) age at referral was 23·9 (0·7) years and mean (SE) forced expiratory volume in one second (FEV_1) was 0·87 (0·04) l. Fourteen patients died whilst awaiting transplantation and 19 received donor lungs. There have been 10 deaths in the transplanted group. Survival following transplantation was 58% at one year and 52% at two years.**

***Conclusion* – Most of the deaths that occurred in the Cystic Fibrosis Clinic were in patients who either were not considered suitable for transplantation or were still awaiting transplantation. Whilst lung transplantation is the focus for many adults with cystic fibrosis, lack of donor organs has limited the impact of transplant programmes on the clinic.**

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Keywords: cystic fibrosis, lung transplantation, survival, *Burkholderia cepacia*.

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Despite great improvements in treatment for cystic fibrosis, nearly all patients will develop respiratory failure so that the only hope of survival is lung transplantation. Heart-lung transplantation for pulmonary vascular diseases was first reported in 1982[1] and the initial experience in transplanting patients with cystic fibrosis was published in 1984.[2] Since 1987 we have been referring suitable candidates for assessment for transplantation. Publications of survival rates following transplantation inform us of progress being made in this field, but do not describe the fate of most of the patients with cystic fibrosis who will not be transplanted. Our experience of referring patients with cystic fibrosis from a single clinic gives a perspective on the impact of transplantation programmes on the adult cystic fibrosis population as a whole.

Respiratory physicians who manage patients with cystic fibrosis need to decide whether, when, and where to refer patients for consideration of transplantation. We have examined our referral practice and patient outcome up to the end of 1994.

Methods

PATIENT SELECTION

Since 1977 the Birmingham Heartlands Hospital (formerly East Birmingham Hospital) Adult Cystic Fibrosis Clinic has managed 192 patients in total. Currently there are 141 patients either receiving sole care or in a shared care scheme with a referring respiratory physician or paediatrician. Most patients are referred to the clinic from within the West Midlands region but a significant number come from other parts of England and Wales. Patients are seen in the outpatient clinic on a regular basis, depending on the severity of their disease, and are admitted to the Adult Cystic Fibrosis Clinic when necessary. Symptoms, body weight, and spirometric parameters are recorded at each visit. Throughout this time the patients are managed by one consultant respiratory physician (DES).

If life expectancy is thought to be less than two years, and respiratory reserve becomes poor (approximately 30% of predicted forced expiratory volume in one second (FEV_1)) and is declining quickly, or frequent infection with prolonged hospital stays occurs, a patient will be counselled about the possibility of referral for lung transplantation. A referral is made if agreement is reached with the patient and relatives where appropriate, and after extensive discussion with the multidisciplinary team. The choice of centre depends upon geographical factors, patient preference, clinical considerations, and our previous experience.

Mean (SE) characteristics of patients studied

	Range	*Men (n=25)*	*Women (n=24)*	*Total (n=49)*
Age	18–44	23·4 (0·7)	24·5 (1·3)	23·9 (0·7)
% Ideal body weight	55·8–114	80·2 (3·1)	83·6 (1·9)	82·0 (1·8)
FEV_1 (l)	0·4–1·65	0·91 (0·1)	0·83 (0·04)	0·87 (0·04)
% predicted FEV_1	10–42	24·7 (2·3)	28·3 (1·4)	26·6 (1·3)
FVC (l)	0·7–3·2	1·88 (0·2)	1·59 (0·1)	1·73 (0·1)
% predicted FVC	15–76	42·3 (4·1)	47·7 (2·5)	45·1 (2·3)
Oxygen saturation (%)	79–97	90 (1·7)	92 (1·0)	91 (0·9)
Pao_2 (kPa)	5·3–11	7·8 (0·4)	8·3 (0·4)	8·1 (0·3)
$Paco_2$ (kPa)	3·5–7·8	5·7 (0·3)	5·0 (0·2)	5·3 (0·2)
Standard bicarbonate (mmol/l)	22–36	28·5 (0·9)	26·0 (0·8)	27·2 (0·6)

FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; Pao_2, $Paco_2$ = arterial oxygen and carbon dioxide tensions.

DATA COLLECTION AND ANALYSIS

We have reviewed the case records of all patients referred for transplantation and all patients who have died since 1987, noting dates of referral, assessment, acceptance or rejection, and transplantation or death.

Results

Between January 1987 and the end of December 1994, 49 patients (24 women) with cystic fibrosis were referred to transplant centres in England for consideration for lung transplantation and 16 patients died without referral. The reasons for non-referral were:

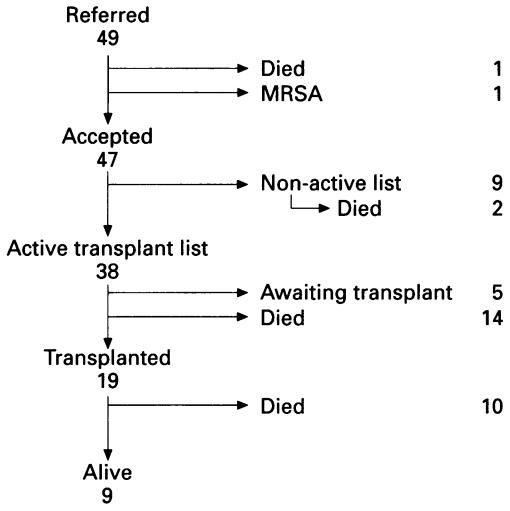

Figure 1 Outcome for all patients referred for lung transplantation from Birmingham Heartlands Adult Cystic Fibrosis Clinic, 1987–94. MRSA = multiple resistant Staphylococcus aureus.

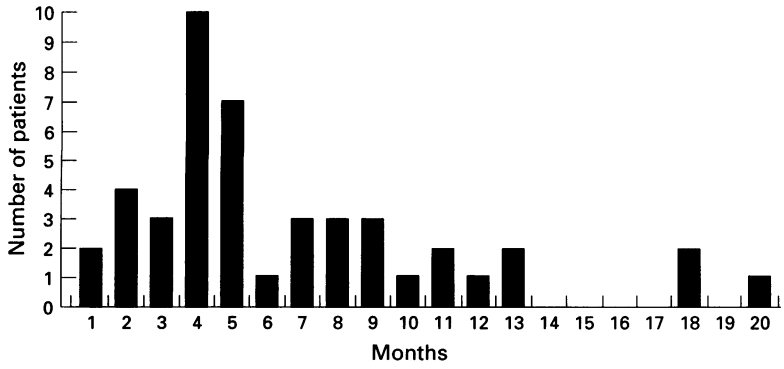

Figure 2 Time from referral for transplantation to assessment.

rapid/unexpected decline (five patients, three of these following acquisition of *Burkholderia (Pseudomonas) cepacia*); referral declined by patient (three); assessed as unsuitable on psychosocial grounds (three); two died whilst still being assessed for dual hepatic and lung transplantation and three died from other causes (suicide, hypoglycaemic coma and acute renal failure related to the treatment of severe pulmonary infection). Most were referred to centres at Papworth (23) and Harefield (17), with a smaller number being referred to Manchester (five), Newcastle (two), and Birmingham (one). One patient had been referred to Great Ormond Street Hospital and subsequently came under our care. The age, lung function, and body weight of the 49 patients are shown in the table.

The rate of decline in lung function for patients referred for transplantation was 160 ml/year in the 12 months before referral compared with 10 ml/year in the following year. The reduction in the rate of decline in FEV_1 following referral for transplantation probably results from the fact that patients are referred at a time of frequent exacerbations and subsequently recover a little of their FEV_1 and a "bottoming out" effect. However, the number of admissions for intravenous antibiotics did not show a significant difference with 2·7 admissions/year in the year before referral and 2·9 admissions/year in the year after referral. In the year before referral analysis of sputum cultures showed that all were colonised by at least one *Pseudomonas* species. Sputum samples of 45 patients grew *Pseudomonas aeruginosa*, six grew *Burkholderia cepacia*, 12 *Staphylococcus aureus*, two *Aspergillus fumigatus* (one in association with an aspergilloma), and one *Streptococcus viridans*.

The outcome for all the patients referred from our clinic is shown in fig 1. One patient was considered unsuitable by the cardiothoracic centre for heart-lung transplantation because of colonisation with multiply resistant *Staphylococcus aureus* and another deteriorated rapidly and died whilst awaiting assessment. In all, 47 patients were accepted onto either the active transplantation list or a provisional list. The waiting time between referral and assessment varied between one and 20 months with an average of 6·6 months and a mode of four months (fig 2). The very long delays in three patients were due to two patients changing their mind twice and cancelling appointments for assessment and in one case the assessment form was misplaced.

At initial assessment 24 of the 47 patients accepted were put on to a provisional list and kept under regular review. Subsequently, 17 of these patients joined the active transplantation list. The average length of time on the non-active list was 12·7 months (24·7 months for those remaining on the list and 6·4 months for those who later joined the active list). Two patients declined rapidly and died whilst on the non-active list.

Fourteen patients on the active waiting list for transplantation died. The mean length of time from referral to death was 15·9 months

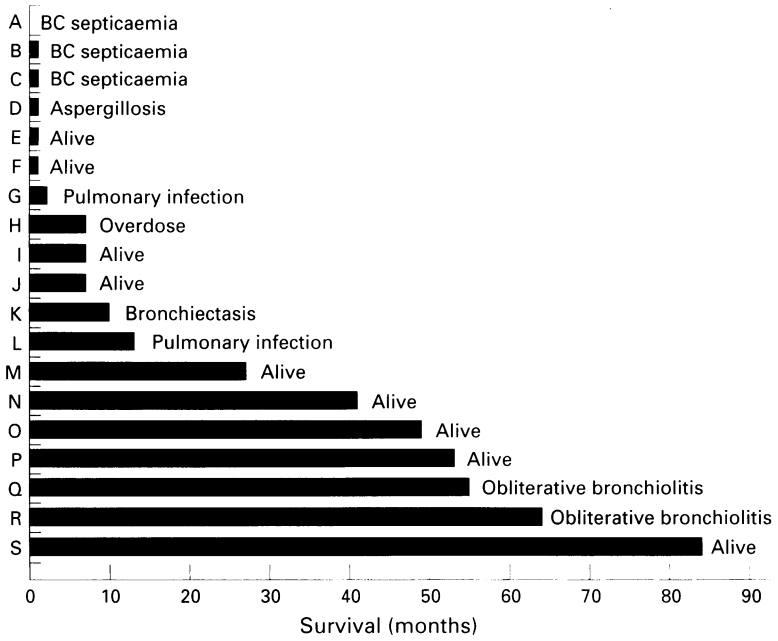

Figure 3 Outcome of lung transplant recipients. BC = Burkholderia cepacia.

(range 3–30), and time on the active list was 8·1 months (range 0·5–25). The five patients remaining on the active transplantation list have waited an average of 17·9 months (range 7–29). Nineteen patients underwent lung transplantation after an average wait on the active list of 9·3 months (range 1–25 months) and mean time from referral to transplantation of 18·8 months (range 9–40).

Ten of the 19 patients who were transplanted have subsequently died and these fell into three main groups. Three patients with *B cepacia* died from *B cepacia* septicaemia within the first postoperative month, four died between one and 14 months after transplantation due to progressive bronchiectasis with recurrent infection, and one had a sudden massive haemoptysis caused by erosion of a pulmonary artery by locally invasive aspergillosis. Two patients died of respiratory failure from obliterative bronchiolitis in their fifth and sixth years after transplantation, respectively. The outcome for the transplanted patients is summarised in fig 3, and the survival rates following transplantation for patients from our clinic are illustrated in fig 4 (58% at one year, 52% at two years).

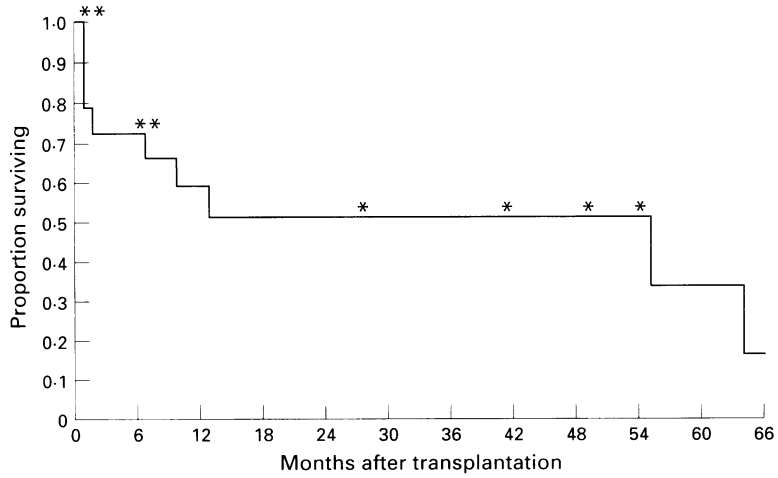

*Figure 4 Survival of lung transplant recipients (Kaplan-Meier plot). * Censored data (patients still alive).*

There are currently nine survivors following transplantation. Four of these are judged to have a good quality of life, and two others were transplanted less than two months ago. Two have poor lung function and are oxygen dependent, and one awaits a renal transplant for cyclosporin-induced renal damage, though lung function is good.

Discussion

Whilst a successful lung transplantation undoubtedly transforms the quality of life for patients with respiratory failure due to cystic fibrosis, we have documented the fate of those patients who are still waiting for transplantation or who have died before transplantation. During the period we have reviewed, 40% of the deaths occurred in patients who had not been assessed for transplantation and a further 37% occurred in patients on an active or holding transplantation waiting list. Thus, the majority of our patients with cystic fibrosis are unlikely to benefit from improved survival following transplantation unless donor organs become more readily available. This information is important if we are to advise potential transplant candidates fully.

Over the period not all patients were suitable for lung transplantation because of psychosocial factors or poor compliance. We have found that a decision not to transplant may have to be reviewed as patients in their teens or early twenties mature. It has been noted previously that inappropriate referral for transplant assessment without adequate discussion can cause unnecessary anxiety and psychological trauma.[3] None of our patients refused transplantation after referral, though one changed her mind during her final illness while remaining physically suitable until a late stage. Referral for transplantation brings stress and it is incumbent upon the referring physicians to ensure that the referral is appropriate. Prior discussion with the transplant centres avoids any unnecessary disappointment.

When to refer is still a difficult decision and there is little guidance. Currently the consensus is that patients should be referred when they have an FEV_1 of 30% or less of predicted[4] and an estimated life expectancy of two years. This is a clinical judgement and in our practice tends to be when patients with an FEV_1 of approximately one litre develop increasingly frequent pulmonary exacerbations requiring antibiotics. In other diseases such as chronic renal failure there are wide variations in referral practice and there is little reason to suppose that this is not the case with lung transplantation for cystic fibrosis. Initially half of our patients went on to a "non-active" list and the remainder went directly on to an active transplantation waiting list. This seems to be reasonable, giving our patients the best chance to be on an active list at the appropriate time without swamping the centres with patients who will not require

a transplant for some years. Furthermore, it has been suggested that for many patients being put on to a non-active list is a very positive experience as it communicates to the patient that the disease has not yet reached a terminal stage and the option of being put on to the active list remains as an "insurance policy". Perhaps every patient should be referred at a time when they are well enough to be on a provisional list, enabling them to transfer to the active list at the ideal time. The ideal time of referral may recede as new treatments such as DNase and assisted ventilation may reduce the rate of decline.[5,6] The promise of gene therapy may further delay the need for lung transplantation.

Sadly, 14 of our patients died whilst awaiting their transplant and two deteriorated quickly and died on the non-active list. Thus, 16 of the 47 patients (34%) accepted for transplantation died before the operation and, in our opinion, all remained eligible for transplantation until shortly before death.

Survival after transplantation for cystic fibrosis in our group was 58% at one year and 52% at two and three years. This is less than that reported from the transplant centres themselves. At Papworth survival was 78% at one year and 65% at three years.[7] Results from Harefield were 69%, 52%, and 49% at one, two and three years, respectively.[8] A small North American study reported 78% survival at one and three years.[9] Direct comparisons between these series and our own is difficult for three reasons: the Harefield and Papworth series contain some Birmingham patients; the other studies quote survival for adults and children; and, lastly, the numbers are relatively small and premature death or prolonged survival in a few patients can have a large effect on the survival rate. Bearing these caveats in mind, it appears that the main reason for lower survival in our group is a high early mortality. We had a higher proportion of patients with *B cepacia* in their sputum before transplantation than was quoted in other series.[8]

Three of the four patients with *B cepacia* who were transplanted died within one month with *B cepacia* septicaemia. Snell in Toronto found that seven of 15 patients who grew *B cepacia* either before or after transplantation also died as a direct result of overwhelming *B cepacia* infection, whereas there were no deaths amongst seven patients who had never grown *B cepacia*.[10] This contrasts with data from the UK centres that suggest that there is no excess risk of death following transplantation when colonised by *B cepacia*.[11] This difference may be due to the earlier occurrence of the epidemic strain in North America, as it is only within the past year that substantial numbers of the British cohort of cystic fibrosis patients colonised by the epidemic strain of *B cepacia* have required transplantation. Indeed, in our small group the first transplant in a patient colonised by *B cepacia* in 1990 was successful whereas the three patients transplanted since 1993 have all died.

A major concern is when patients deteriorate and a decision has to be made to continue with intensive medical therapy or to "switch" to palliative care. The counselling process which takes place before referral for transplantation needs to include a realistic appreciation of the risks as well as the great benefits of a successful outcome. Physicians need to be mindful that patients may pass through their "window of opportunity" and be prepared to provide support and comfort before their patient's death. Whether to ventilate such patients in the hope that a transplant will be available in the immediate future is a complex issue and is best discussed with the transplantation centre and the patient. In our experience this has been a fruitless exercise. The temptation to "keep going" may deny a dying patient comfort and time to accept death.

Lung transplantation provides new hope for cystic fibrosis patients with progressive deterioration in lung function. Many patients will not live long enough to be found a suitable donor because of competition for a limited supply of organs. In these circumstances patients and staff need to be informed of the likely outcome for all patients awaiting lung transplantation.

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